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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/169,048	10/08/98	HUSE W	P-IX-3280

EXAMINER	
GARCIA, M	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/169,048	Huse et al
Examiner	**Art Unit**
Maurie E. Garcia, Ph. D.	1627

-- The MAILING DATE of this communicati n appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *THREE* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 25, 2001*

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-39* is/are pending in the applica

4a) Of the above, claim(s) *1-9 and 19-38* is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *10-18 and 39* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

1. Applicant's Response filed May 25, 2001 (Paper No. 17) is acknowledged. Claim 39 was added, claims 10, 11, 13, 14, 17 and 18 were amended and no claims were cancelled. Therefore claims 1-39 are pending.

2. This application contains claims 1-9 drawn to an invention nonelected with traverse in Paper No. 14. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01. Note that this application also contains claims 19-38 drawn to an invention nonelected *without* traverse in Paper No. 14 (see previous action).

3. Newly added claim 39 reads on the elected invention. Therefore, claims 10-18 and 39 are examined on the merits in this action.

Withdrawn Objections/Rejections

4. The previous objection to the disclosure is withdrawn in view of applicant's amendments thereto. The rejection of claim 17 under 35 U.S.C. 112, second paragraph is also withdrawn in view of applicant's amendments thereto. The previous rejection under 35 USC 102 over Wilson-Lingardo et al is withdrawn in view of applicant's amendments. A new rejection necessitated by applicant's amendments is also set forth below.

Maintained Rejections

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 10-18 and newly added claim 39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. Applicant's claims are directed to a method of determining binding of a "ligand" to one or more "receptors". The claims use generic terminology such as "collective ligand variant population", "binding activity" and "optimal binding affinity". These terms are defined in the instant disclosure but the definitions are very broad.

The specification discloses **no** examples of carrying out such a method (the only example given appears to be for the opposite case scenario). These ligands and receptors could encompass very different moieties such as peptides, oligonucleotides or other organic molecules. Also, claims 15 and 16 require specific techniques of producing the ligands (recombinant expression in melanophore cells) and claim 17

and newly added 39 require tagging. None of these techniques are adequately described in the instant disclosure. There are **no** examples of producing ligands by recombinant expression in melanophore cells and **no** examples of tagging such ligands whatsoever.

Thus, the disclosure simply does not provide adequate support to show possession of the claimed invention. The disclosure is neither representative of the claimed genus, nor does it represent a substantial portion of the claimed genus. Moreover, the claimed genus encompasses members which are yet to be prepared or envisioned. This further evidences that instant disclosure does not constitute support for the claimed genus or a substantial portion thereof.

Response to Arguments

7. Applicant's arguments filed May 25, 2001 have been fully considered but are not found persuasive. The examiner's rationale is set forth below. Please also see Response to Arguments set forth in paragraphs 15-19 below.

8. Applicant argues that the claims are adequately described and sets forth various citations/definitions from the instant specification concerning the terms discussed in the rejection (see Response, pages 5-9). The examiner acknowledged these definitions in the rejection above but stated that they were *very broad.* The "collective ligand variant population" recited in the claims could encompass a virtually unlimited number of compounds. This is because the instant claims give ***no structure*** for the ligand itself and no

structural information as to the specific "variant". Thus the claims could encompass an infinite number of variations. As also stated above, the examiner pointed out that the specification discloses **no** examples of the claimed "collective ligand variant population".

9. Applicant argues that no working examples are necessary and that the provided example (which is for the opposite case scenario than what is instantly claimed), provides adequate support (see Response, page 8). While an example is indeed not required, lack of a working example, however, is a factor to be considered, especially in a case involving an unpredictable and undeveloped art (see below). Also, one of ordinary skill would not necessarily expect to be able to extrapolate the disclosed example (to the opposite case scenario) as far as its applicability to the instant claims.

10. Also, the examiner deems the art to be unpredictable. The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Additionally, the Board has held on the issue of unpredictability that "... the unpredictability of an art area alone may be enough to create a reasonable doubt as to the accuracy of statements in the specification." *Ex parte Singh*, 17 U.S.P.Q.2d 1714,1716 (B.P.A.I. 1990).

11. With respect to adequate disclosure of the scope of the presently claimed generic applicant is referred to the discussion in *University of California v. Eli Lilly and Co.* (U.S. Court of Appeals Federal Circuit (CAFC) 43 USPQ2d 1398 7/22/1997 Decided July 22, 1997; No. 96-1175) regarding disclosure. For adequate disclosure, like enablement, requires representative examples which provide reasonable assurance to one skilled in the art that the compounds falling within the scope both possess the alleged utility and additionally demonstrate that applicant had possession of the full scope of the claimed invention. See *In re Riat* (CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr* (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and *University of California v. Eli Lilly and Co* cited above (for disclosure). The more unpredictable the art the greater the showing required (e.g. by "representative examples") for both enablement and adequate disclosure. Again, no working examples reading on the instant claims have been provided.

12. Lastly, an objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). The examiner maintains because of the breadth of the claims, the unpredictability of the art and the lack of any working examples the above standard is not met. Thus the above rejection of claims 10-18 and newly added claim 39 under 35 U.S.C. 112, first paragraph is maintained.

13. Claims 10-18 and newly added claim 39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the level of one of ordinary skill;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The breadth of the claims and the nature of the invention: The claims are drawn to a method of determining binding of a "ligand" to one or more "receptors". No limitations on the specific structure of the ligand or receptor are given and, as such, this could read on a wide variety of structures. The invention is such that each of the components must be present in operable form for successful practice of the invention. For example, the ligand must bind the receptor and the binding must be able to be detected. The state of the prior art and the level of predictability in the art:

Ligand/receptor binding pairs were well-known in the art at the time of the invention (see art rejections below); however, only limited numbers of such pairs were known and the specification gives no guidance to permit one of skill in the art to devise strategies for synthesis of *any* such pair of molecules. The structures of possible variants are sufficiently diverse that one of ordinary skill would not be able to predict their structures. Also, claims 15 and 16 require specific techniques of producing the ligands (recombinant expression in melanophore cells) and claim 17 and newly added 39 require tagging. All of these techniques are unpredictable in the art. One of ordinary skill would not know, a priori, how to make such a ligand by the claimed method and also how to tag such a ligand with an "identifiable tag". Specifically, in regard to claims 15 and 16, it was known in the art at the time of filing how to make *receptors* using melanophore cells (see US 5,462,856, on PTO-1449, Examples 1-6 and claims), but not how to make *ligands* in such a manner. With regard to claim 17, adding tags to the ligands adds to the unpredictability of the claimed method since this type of synthesis requires high efficiency and is further complicated by carryover, cross-reactions, etc., all of which are acknowledged issues in the art. Each must be dealt with in the optimization of a synthesis scheme. A review article published by Janda discusses these issues (see Proc. Natl. Acad. Sci. Vol. 91 pp. 10779-10785, November 1994. See especially page 10782-10785). The level of one of ordinary skill: The level of skill would be high, most likely at the Ph.D. level. The existence of working examples and the quantity of experimentation needed to make or use the invention based on the content of the disclosure: Applicants have provided **no**

working examples of the claimed method, for both the generic embodiments (claims 10-14 and 18) or the specific embodiments (claims 15-17 and newly added 39). The state of the prior art is such that one of ordinary skill could not predict how to produce the required ligands and receptors and practice the claimed method of determining binding as required by the instant claims. Therefore further research would be necessary to make or use the invention and it would require undue experimentation to carry out the invention as claimed.

Response to Arguments

14. Applicant's arguments filed May 25, 2001 have been fully considered but are not found persuasive. The examiner's rationale is set forth below. Please also see Response to Arguments set forth in paragraphs 8-12 above.

15. Applicant argues that the claims are enabled and sets forth various citations/definitions from the instant specification concerning the terms discussed in the rejection (see Response, pages 10-12). However, the terms/methods described by applicant are set forth in only the broadest terms. As stated in the rejection, no limitations on the specific structure of the ligand or receptor are given and, as such, this could read on a wide variety of structures. The invention is such that each of the components must be present in operable form for successful practice of the invention. For example, the ligand must bind the receptor and the binding must be able to be detected.

16. As stated above (paragraph 10), the examiner deems the art to be unpredictable. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved. See *In re Fisher*, 57 CCPA 1099,427 F.2d 833,839,166 USPQ 18,24(1970). Additionally, the Board has held on the issue of unpredictability that "... the unpredictability of an art area alone may be enough to create a reasonable doubt as to the accuracy of statements in the specification." *Ex parte Singh*, 17 U.S.P.Q.2d 1714,1716 (B.P.A.I. 1990).

17. Applicant argues that the instant specification provides sufficient teachings regarding structure and function of the claimed "collective ligand variant population" (see, for example, Response page 10 bottom through page 11, top). However, the examiner's position is that the instant specification does not provide to one skilled in the art a reasonable amount of guidance with respect to the direction in which the experimentation should proceed in making and using the claimed invention. Most importantly, ***the instant specification fails to identify that structure which is required for the claimed activity***. In the absence of such guidance, a practitioner of the art would have to resort to a substantial amount of experimental trial and error to produce a "collective ligand variant population" that has the required functional limitations. This trial and error would clearly constitute undue experimentation.

18. Applicant also argues that one of ordinary skill would know how to tag the claimed ligands. The examiner respectfully disagrees as such processes were unpredictable and highly dependent on compound structure (as evidenced by the cited Janda reference). Again, ***no structure*** for the instant "collective ligand variant population" is provided. Note that "if there is no disclosure of any starting material or of any conditions under which claimed process can be carried out, undue experimentation is required, and there is failure to meet enablement requirement that cannot be rectified by asserting that all disclosure related to process is within skill of art." *Genentech Inc. v. Novo Nordisk A/S* (CA FC) 42 USPQ2d 1001 (3/13/1997)

19. Please also note that arguments of counsel alone cannot take the place of evidence in the record once an examiner has advanced a reasonable basis for questioning the disclosure. See *In re Budnick*, 537 F.2d at 538, 190 USPQ at 424; *In re Schulze*, 346 F.2d 600, 145 USPQ 716 (CCPA 1965); and In re Cole,326 F.2d 769, 140 USPQ 230 (CCPA 1964). For example, in a case where the record consisted substantially of arguments and opinions of applicant's attorney, the court indicated that factual affidavits could have provided important evidence on the issue of enablement. See *In re Knowlton*, 500 F.2d at 572, 183 USPQ at 37, and *In re Wiseman*,596 F.2d 1019, 201 USPQ 658 (CCPA 1979).

Claim Rejections - 35 USC § 102

20. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States

21. Claims 10-14, 17 and 18 remain rejected under 35 U.S.C. 102(b) as being anticipated by Combs et al (JACS, January 1996, Vol. 118, No. 1, pp. 287-288).

Combs et al disclose a method for using a "a library of ligands that direct non-peptide binding elements into the specificity pocket of SH3 proteins" (see Figure 1). These ligands comprise two binding sites; "a common low affinity biasing sequence PLPPLP" and 32 "capping reagents" that have the potential to bind in the specificity pocket (see page 287). The SH3 domain from the protein kinase Src is the receptor. The compounds were assayed against this receptor and at least 7 ligands were identified that bind (see Figure 3 and Table 1). Ligand 1A was also measured against the SH3 domain in the p85 component of PI3K and did show binding for this domain (a second receptor), although it showed selectivity for Src SH3 (see page 288, 2nd column).

The reference discloses that the compounds of the library were tagged and then decoded to find an optimal binding ligand (Figure 3 and Table 1) and the binding of the library compounds (ligands) to the receptor was performed in three stages (see page 287, 2nd column, bottom and Supplemental pages 1-3). This reads directly on the limitations of the instant claims 11-14, 17 and 18.

Response to Arguments

22. Applicant's arguments filed May 25, 2001 have been fully considered but are not found persuasive. The examiner's rationale is set forth below.

23. Applicant argues that Combs et al does not disclose the claimed invention because it dose not teach contacting/binding to two or more receptors (Response, pages 13-14). However, as set forth above, the reference clearly discloses that Ligand 1A was also measured against the SH3 domain in the p85 component of PI3K and did show binding for this domain (***a second receptor***), although it showed selectivity for Src SH3 (see page 288, 2nd column of the reference). Thus Combs et al discloses that two receptors (PI3K and Src) were contacted and binding was tested for both.

New Rejections -- Necessitated by Amendment

Claim Rejections - 35 USC § 112

24. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

25. Claims 10-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The specification as originally filed does not provide support for the invention as now claimed. Applicant has changed the limitation "one or more receptors" to "two or more receptors" in the Response filed May 25, 2001. After close inspection of the instant specification, the examiner deems that this change is not supported. The examiner does not believe there is sufficient support for the *specific* recitation of "two or more receptors". Applicant points to page 9, lines 26-28 of the instant specification; however, this is dealing only with the size of the population, not the number of receptors it binds

The question is what applicants had possession of at the time of filing. There is no indication in the instant case that applicants had possession of the concept of the claimed "collective ligand variant population" binding to "two or more receptors".

An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). It is completely unclear that the description as filed supports the added limitation of binding "two or more receptors". Note that a broad generic disclosure is **not** sufficient support for a *specific* entity within the class.

In accordance with MPEP § 714.02, applicants **should specifically point out support** for any amendments made to the disclosure.

Status of Claims/ Conclusion

26. No claims are allowed.

27. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

28. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maurie E. Garcia, Ph.D. whose telephone number is (703) 308-0065. The examiner can normally be reached on Monday-Thursday and alternate Fridays from 9:30 to 7:00.

29. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat, can be reached on (703) 308-2439. The fax phone number for

the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

DR. JYOTHSNA VENKAT PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Maurie E. Garcia, Ph.D.
August 13, 2001